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**Selective blockade of 2-arachidonoylglycerol hydrolysis produces cannabinoid behavioral effects.**

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**Public Summary:**

2-Arachidonoylglycerol (2-AG) and anandamide are endocannabinoids that activate the cannabinoid receptors CB1 and CB2. Endocannabinoid signaling is terminated by enzymatic hydrolysis, a process that for anandamide is mediated by fatty acid amide hydrolase (FAAH), and for 2-AG is thought to involve monoacylglycerol lipase (MAGL). FAAH inhibitors produce a select subset of the behavioral effects observed with CB1 agonists, which suggests a functional segregation of endocannabinoid signaling pathways in vivo. Testing this hypothesis, however, requires specific tools to independently block anandamide and 2-AG metabolism. Here, we report a potent and selective inhibitor of MAGL called JZL184 that, upon administration to mice, raises brain 2-AG by eight-fold without altering anandamide. JZL184-treated mice exhibited a broad array of CB1-dependent behavioral effects, including analgesia, hypothermia and hypomotility. These data indicate that 2-AG endogenously modulates several behavioral processes classically associated with the pharmacology of cannabinoids and point to overlapping and unique functions for 2-AG and anandamide in vivo.

**Scientific Abstract:**

2-Arachidonoylglycerol (2-AG) and anandamide are endocannabinoids that activate the cannabinoid receptors CB1 and CB2. Endocannabinoid signaling is terminated by enzymatic hydrolysis, a process that for anandamide is mediated by fatty acid amide hydrolase (FAAH), and for 2-AG is thought to involve monoacylglycerol lipase (MAGL). FAAH inhibitors produce a select subset of the behavioral effects observed with CB1 agonists, which suggests a functional segregation of endocannabinoid signaling pathways in vivo. Testing this hypothesis, however, requires specific tools to independently block anandamide and 2-AG metabolism. Here, we report a potent and selective inhibitor of MAGL called JZL184 that, upon administration to mice, raises brain 2-AG by eight-fold without altering anandamide. JZL184-treated mice exhibited a broad array of CB1-dependent behavioral effects, including analgesia, hypothermia and hypomotility. These data indicate that 2-AG endogenously modulates several behavioral processes classically associated with the pharmacology of cannabinoids and point to overlapping and unique functions for 2-AG and anandamide in vivo.

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